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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/648,896	08/25/2000	Jeffrey L. Cleland	P0998D2	6985

7590 04/10/2003

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South San Francisco, CA 94080

EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 04/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/648,896	CLELAND ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-34 and 37-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,28-34 and 37-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14,15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed 1/8/2003 (paper no 13) is acknowledged and entered into the record. Accordingly, no claims have been added or canceled.

2. Claims 26, 28-34, and 37-51 are pending and examined on the record.

Information Disclosure Statement

3. The Information Disclosure Statements filed 1/23/2003 and 2/27/2003 (paper no. 14 & 15) are acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

4. The rejection of claims 26, 28-34, and 37-51 under 35 USC 112, 1st paragraph as lacking an enabling disclosure is maintained for the reasons of record. Applicant argues that the instant application enables the therapy of endometrial, lung, colon, and bladder cancer using anti-HER2 antibodies that are similar to 4D5 (Herceptin) and specifically directs to page 24 lines 11-16. Applicant also argues that the art at the time of filing also teaches that other anti-HER2 antibodies that could inhibit the growth of cancer cells expressing HER2 and concludes that in combination with the teachings of the instant specification, one of skill would have been able to practice the instantly claimed invention. Applicant lastly argues that the skilled artisan would not use antibodies such as N28 as taught by Stancovski *et al* because the specification teaches to use "therapeutically effective" antibodies. Applicant's arguments have been carefully considered but are not found persuasive for the following reasons.

First, applicant points to specific page and line to further clarify the use of any and all anti-HER2 antibodies allegedly enabled by the specification. However, upon review of the specified page the specification provides little evidence of enabling any and all anti-HER2 antibodies that are similar to 4D5, but rather provides a generalized description of an antibody that is able to treat various types of cancers. This is not seen as enabling any and all forms of anti-HER2 antibodies.

Second, applicant directs the examiner to the Shepard *et al* reference (specifically tables I & II) and states that at the time of filing other antibodies were shown to be therapeutically effective in inhibiting growth of cancers. However, upon review of the Shepard *et al* reference, specifically tables I and II, it is noted that not all HER2 antibodies are effective in the inhibition of tumor cell proliferation/ growth. For example, the 6E9 antibody, which showed moderately exposed bands by ELISA, had little effect in the inhibition of tumor cell over control antibodies. Furthermore, upon closer examination of the Shepard *et al* reference, the ability of other anti-HER2 antibodies to inhibit the growth of different cell lines expressing varying amounts of HER2 was examined. Table III indicates that in a cell line expressing the highest levels of HER2, 2 of 6 antibodies showed little difference in inhibiting cellular proliferation when compared to cell lines lacking the HER2 receptor indicating that not all HER2 antibodies are functionally equivalent.

And lastly, the applicant argues that the antibody taught by Stancovski *et al* would not have eroded the ability of the skilled artisan to use any and all antibodies to HER2 because the specification teaches the use of a therapeutically effective antibody.

However, the claims do not recite any specific limitation that would necessarily exclude from the HER2 antibodies the stimulatory antibody taught by Stancovski *et al*. Stancovski *et al* specifically states that "different mAbs to the same protooncogene receptor may have opposing effects" and further states that careful selection must be made when choosing the appropriate mAb. Therefore, other stimulatory antibodies to HER2 may exist. Hence, one of skill in the art would be forced into large amounts of experimentation to practice the instant invention because there is a possibility that the antibody used in the instant invention may have stimulatory effects and hence cuase more harm than good in the treatment of a subject. As such, the specification has only enabled the use of 4D5/Herceptin for the treatment of cancers formulated with lyoprotectants and bulking agents.

Claim Rejections Maintained- 35 USC § 103

5. The rejection of claims 26, 28,37-43, and 51 under 35 USC 103 (a) as being obvious over Shepard *et al* in view of Draber *et al* , Sato *et al* , Nielsen *et al*, Natali *et al*, and Roy *et al* is maintained for the reasons of record. Applicant argues that the molar ratios used in the instant invention are not obvious over the prior art because the prior art teaches a molar ratio that is higher than that taught in the instant invention, and that using a lower ratio of lyoprotectant would not constitute routine optimization. Applicant's arguments have been carefully considered but are not found persuasive. It is noted that the applicant has provided calculations to support the lower amounts of lyoprotectant added to the antibody, however, these are unsupported assertions because the calculations are based on weight per volume, wherein the claims are drawn to molar

amounta. Furthermore, there is no unexpected result achieved from lowering the amount of lyoprotectant to protein, because in the end, the protein was preserved and then re-constituted to active form upon the addition of an aqueous solution. Because all proteins are different and have different molecular weights, the amount of lyoprotectant needed to protect the protein from being damaged in the preservation process may vary, one of skill in the art would have been motivated to play with the ranges so as to minimize the amount of lyoprotectant added to an antibody formulation that is ultimately to be administered to a subject. Therefore, the rejection is maintained because the prior art provided sufficient motivation to practice the instant claimed invention with an antibody formulation that comprises varying ranges of lyoprotectant.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
April 7, 2003